

## Early Diagnosis of Cancer

### Using Genetic Susceptibility for precision prevention and screening

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Queen Mary University of London  
**Clinical Lead for Cancer Genomics**, 100,000GP, Genomics England  
**Honorary Consultant in Clinical Cancer Genetics**, Guys, Barts, Marsden

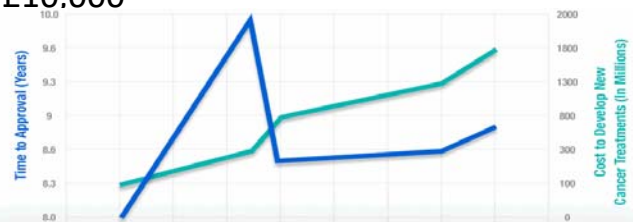
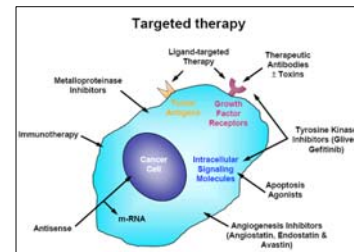
### Fact 1: Patients presenting with advanced cancer die of their cancer and are very expensive to treat

- Patients presenting with advanced cancer (largely) die of their cancer
- Very high treatment costs in final months of management of advanced cancer
  - Drugs
  - Investigations
  - Outpatient appointments
  - Inpatient stay
  - Palliative/hospice care



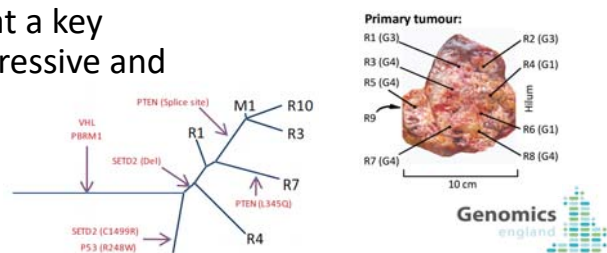
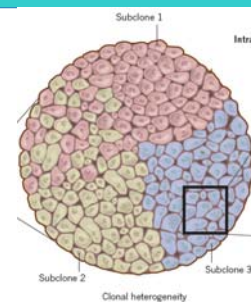
## Fact 2: Sophisticated cancer drugs are used in the setting of advanced cancer to extend life

- (Nearly) all drugs developed over last 10 years have been for use in the advanced setting.
- These drugs do not cure patients of their cancer.
  - These only extend life usually by (median of) months (and sometimes not)
- These 'targeted' drugs may cost > £10,000 per treatment round



## Fact 3: Cancer is ruthlessly Darwinian and evolves against the selective pressure of drugs

- Tumours are clonal, with molecularly distinct subclones
  - Apply a **drug** → create a **selective pressure** → resistance mutation occurs
  - resistant subclone has selective advantage → resistant subclone expands
  - Cancer progresses
- Evolutionary modelling suggests that a key mutational event is followed by aggressive and unbridled cellular replication



## Fact 4: Surgery cures cancers if caught in time

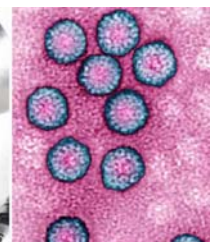
- When a patient is cured of cancer, it is (typically) their surgery which has cured them.
- To clear a tumour by surgery, you must catch it:
  - When it is small (enough),
  - When it is localised
  - Before it bolts



Genomics  
england

## Fact 5: Earlier detection across the population enables more frequent successful surgical resection

- Early detection → Enabling **cure** → **reduced costs**
  - Even better than Early Detection is **Prevention**
1. Delivery of effective screening programmes
  2. Public Education around uptake of screening, symptom awareness
  3. Public Health Interventions around life-style change
  4. Expansion/development vaccine programmes
  5. Expansion of chemoprevention



## Fact 6: Targeting sub-populations at elevated risk will improve early detection and prevention

We currently focus screening efforts by:

- **Age**
  - Breast (50→70)
  - Colorectal (55, 60→74)
  - Cervical (25-64)
- **Gender**

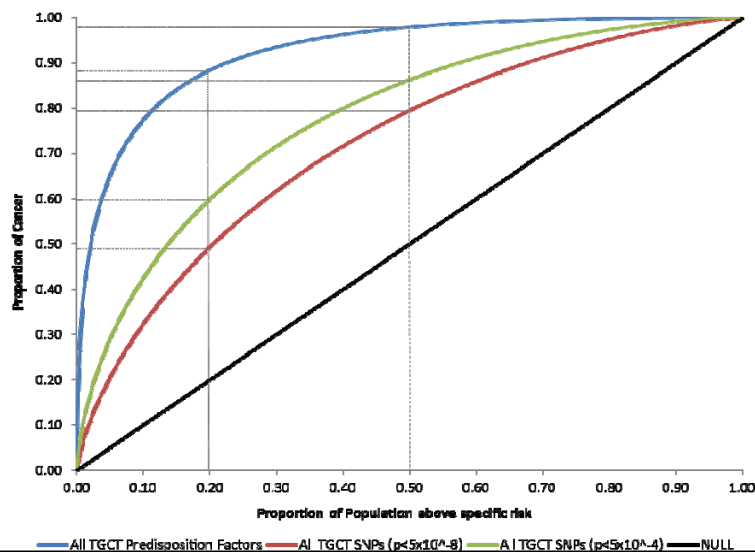
Can we use:

- **genetics?**
- **non genetic (lifestyle) factors**

to further get better bang for buck on screening and prevention by focusing on those at higher risk?



## The majority of cancer arises in the genetically predisposed



# We have known about genetic cancer susceptibility for many centuries

**FAMILY G.**

Cancer Stomach or Intestine. No Cancer in Family.

Legend: L - Living, M - Normal, Op - Operated, Carc - Carcinoma.

THE ARCHIVES OF INTERNAL MEDICINE

HEREDITY WITH REFERENCE TO CARCINOMA

AS SHOWN BY THE STUDY OF THE CASES EXAMINED IN THE PATHOLOGICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN, 1895-1913 \*

ALFRED SCOTT WARTHIN, M.D.

ANN ARBOR, MICH.

# Lynch Syndrome: a genetic condition conferring a ~80% lifetime cancer risk

*Arch Intern Med—Vol 117, Feb 1966*

## Hereditary Factors in Cancer

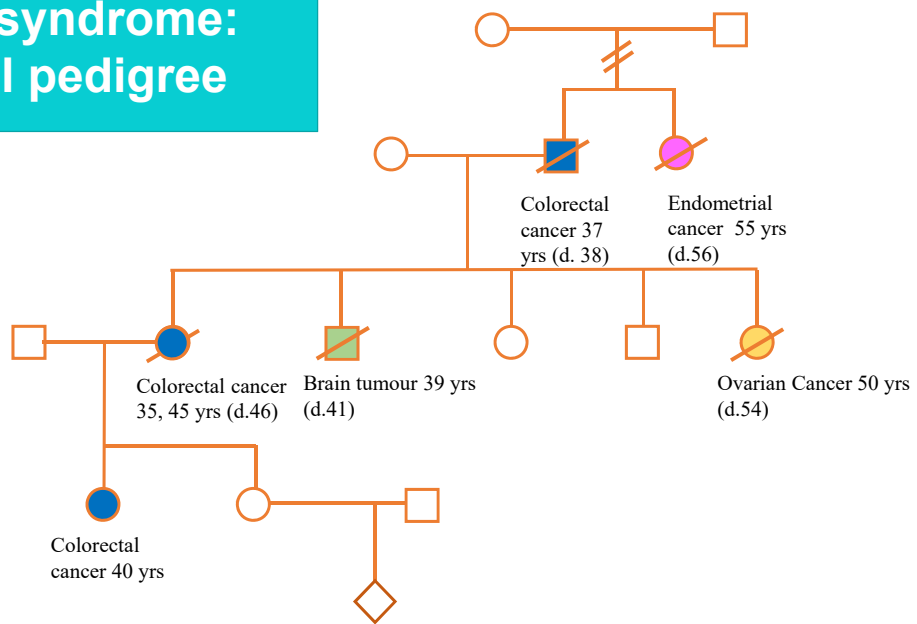
*Study of Two Large Midwestern Kindreds*

H. T. LYNCH, MD, OMAHA; M. W. SHAW, MD, ANN ARBOR, MICH;  
C. W. MAGNUSON, MD; A. L. LARSEN, MD;  
AND A. J. KRUSH, MS, OMAHA

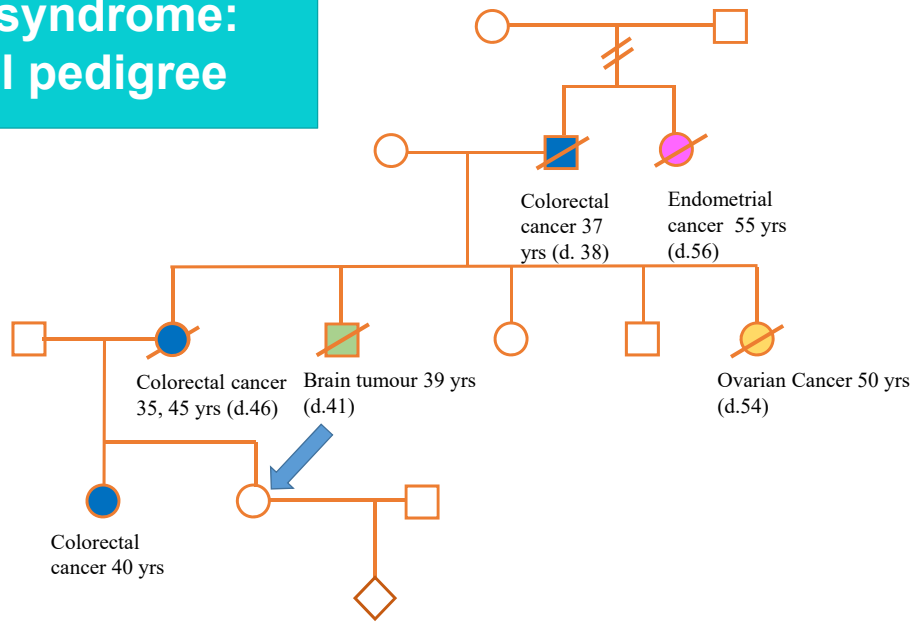
- **Colorectal, endometrial, ovarian, other gastrointestinal cancers, renal tract tumours (transitional epithelium), brain tumours, sebaceous adenomas/carcinomas**
- **MLH1, MSH2, MSH6, PMS2 mutations**
- **Defect in base excision repair**

Mutation	Approximate Incidence at Age 70
MLH1	~75%
MSH2	~80%
MSH6	~25%
PMS2	~20%

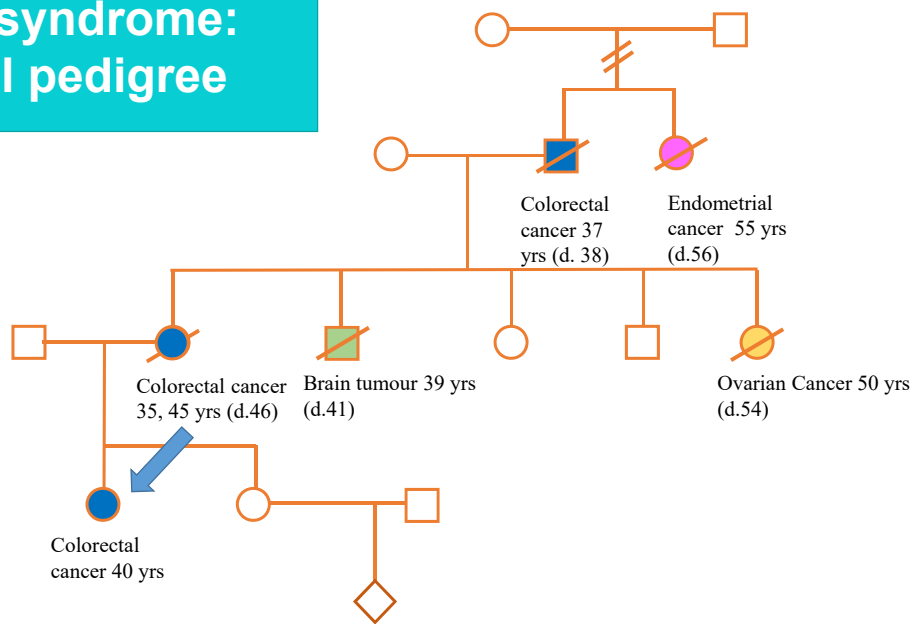
**Lynch syndrome:  
Typical pedigree**



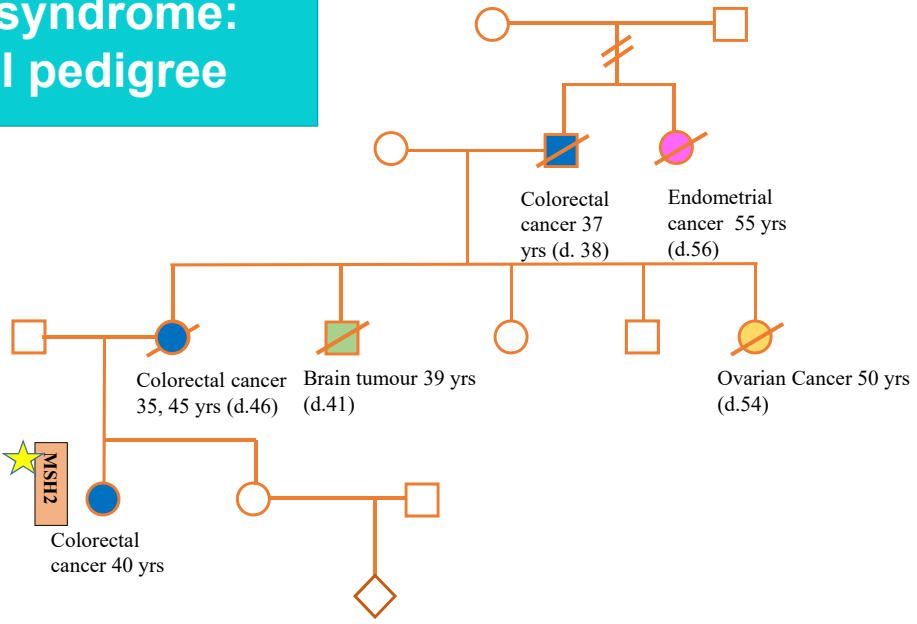
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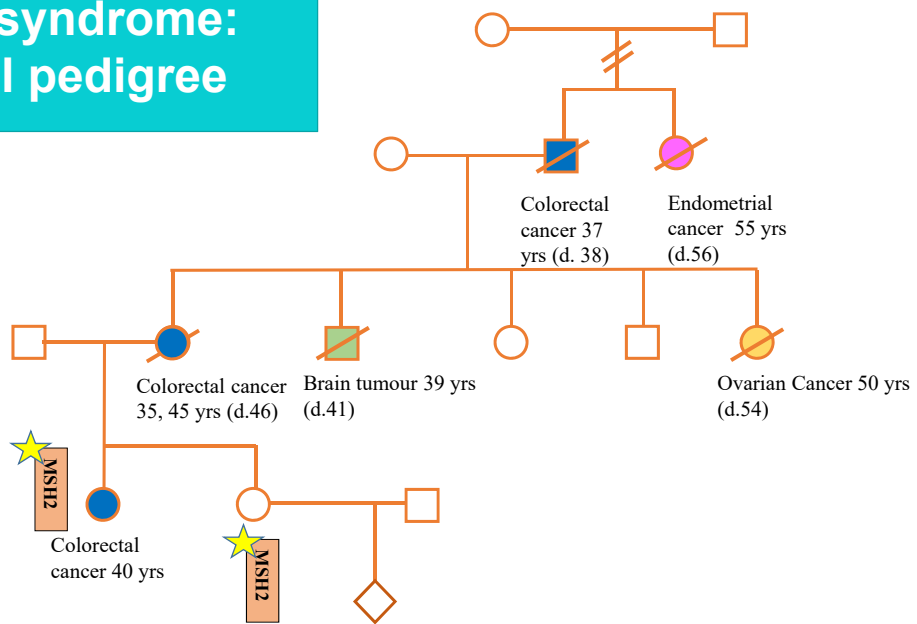
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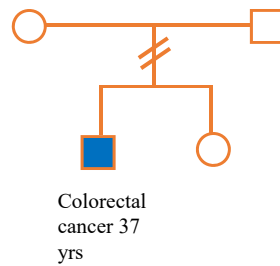
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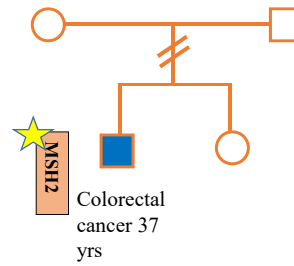


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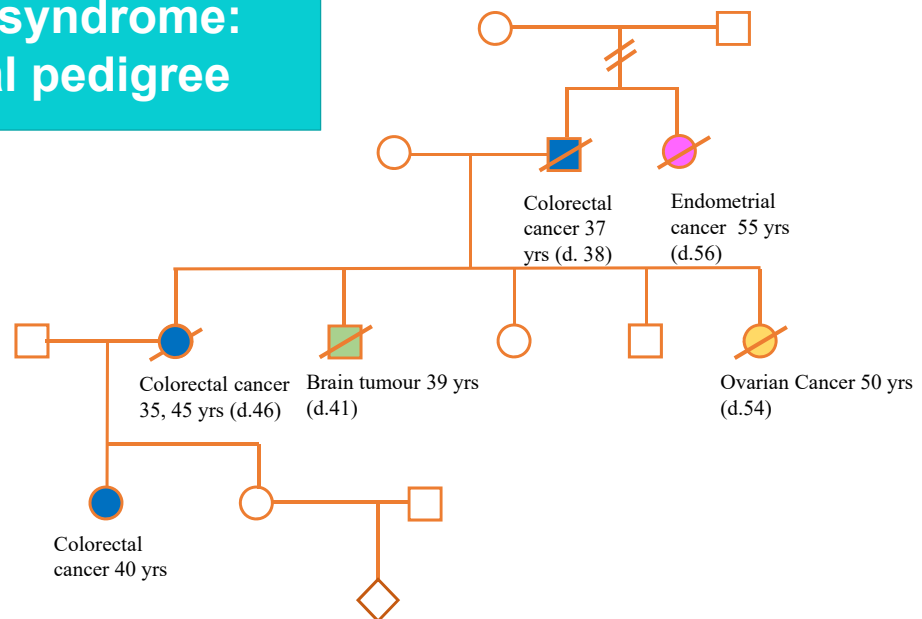




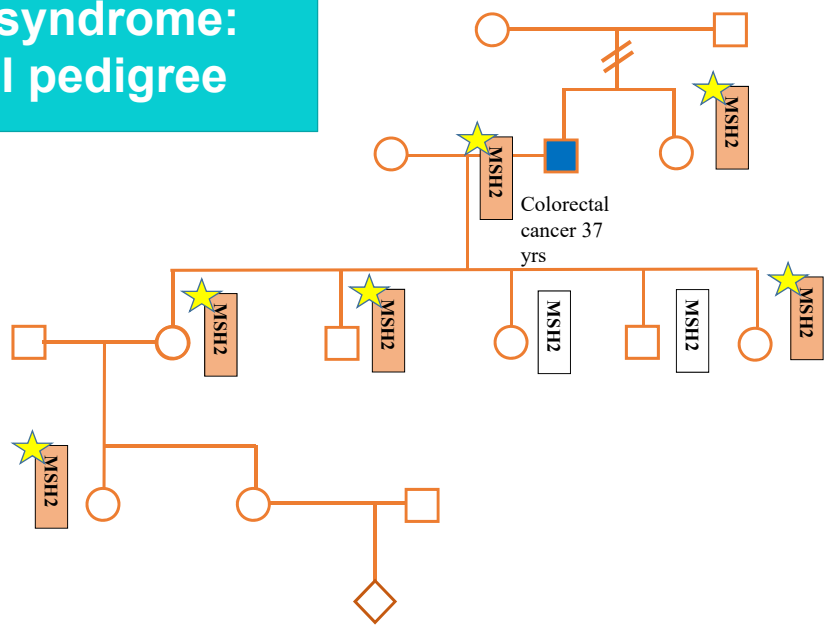
## Lynch syndrome: Typical pedigree



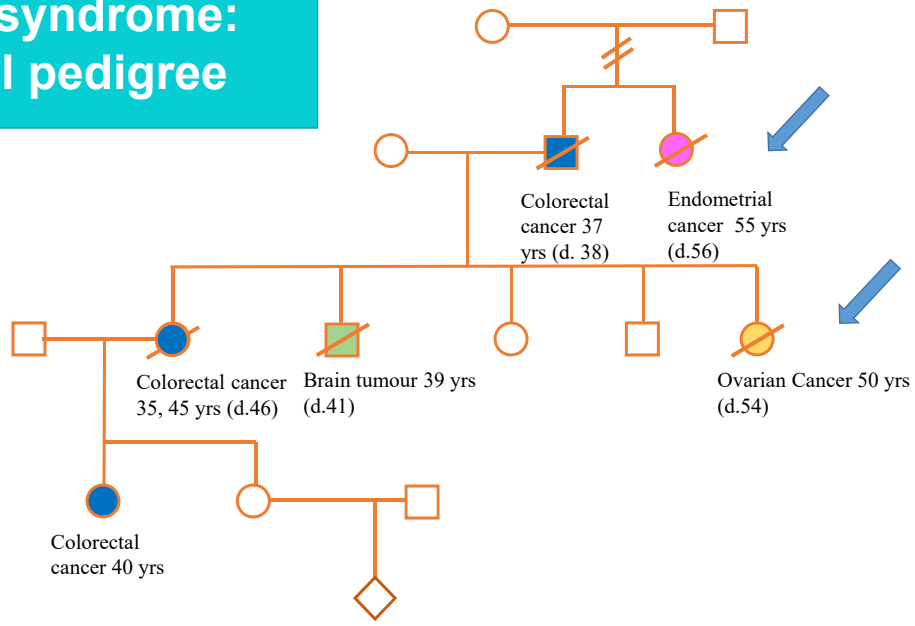
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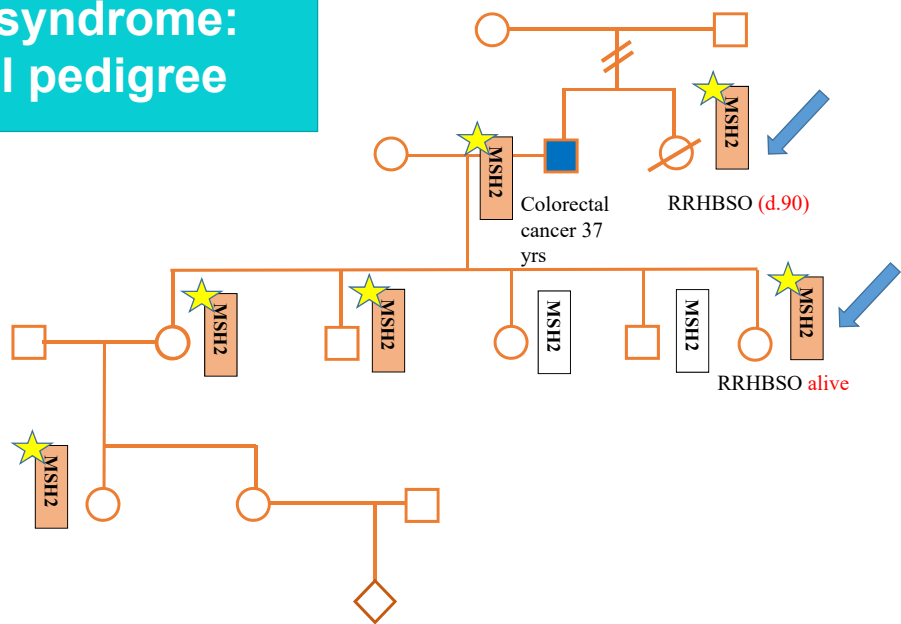
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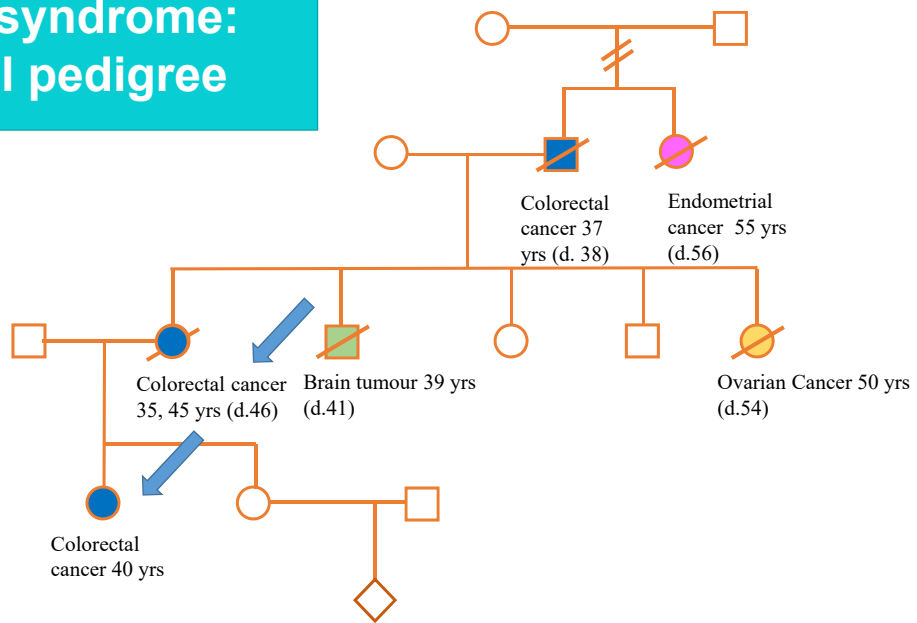
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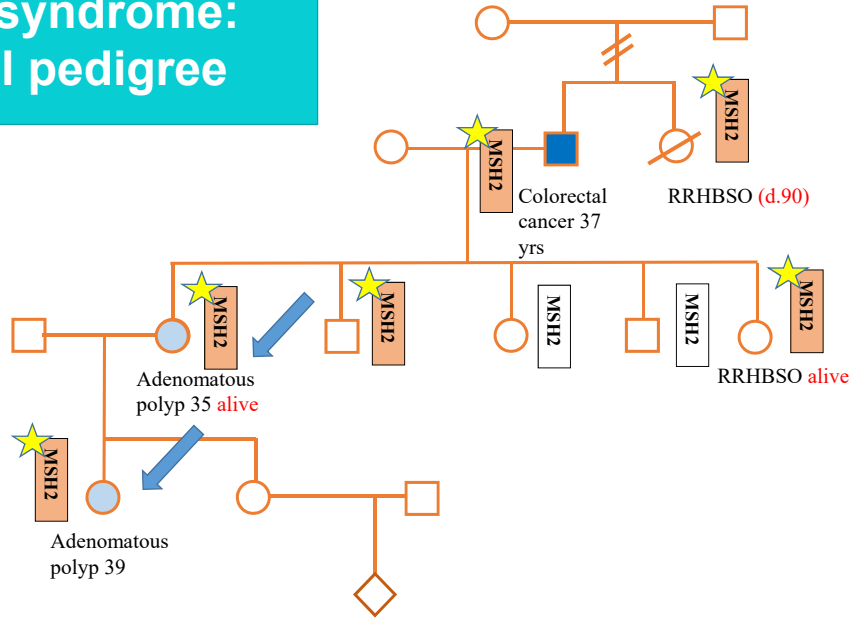
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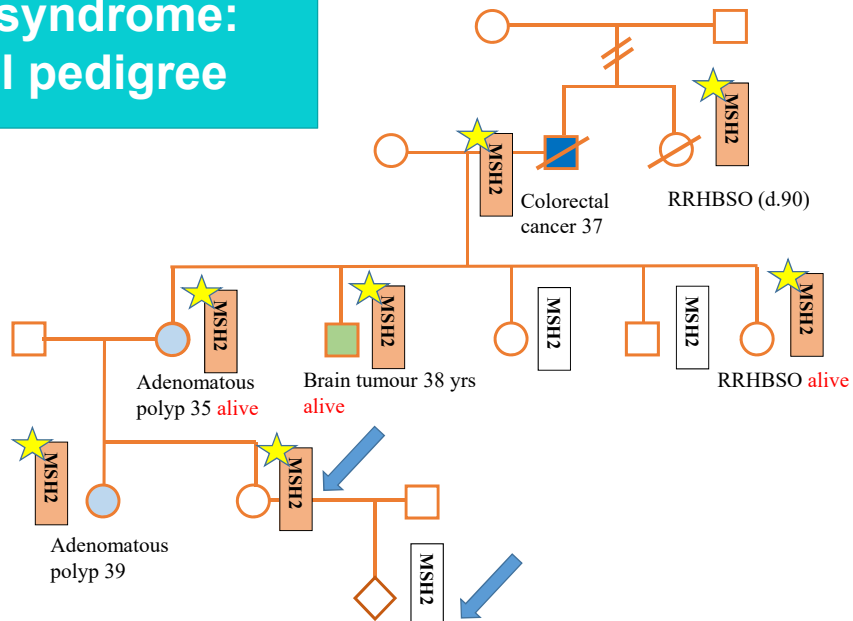
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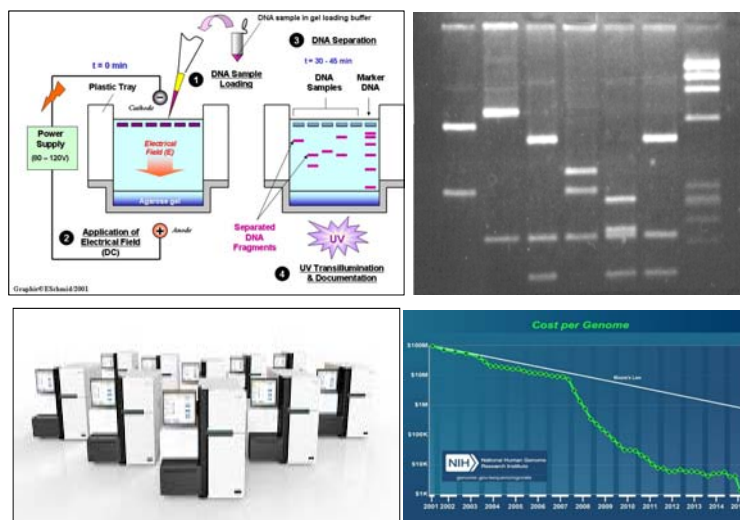
## Next Generation Sequencing: cheaper, rapid, high-throughput,

- **HISTORICALLY** Manual genetic sequencing technologies

- Low throughput, expensive
- Slow, insensitive

- **NOW:** Next Generation Sequencing

- Cheap, high throughput
- Sensitive, rapid TAT
- Reduce 'thresholds' and expand genetic testing



## Screening, Early Detection, Prevention saves lives in Lynch Syndrome

### SCREENING AND EARLY DETECTION

- Colonoscopy every 18 months from age 25
- Endometrial, ovarian screening

### PREVENTION SURGERY

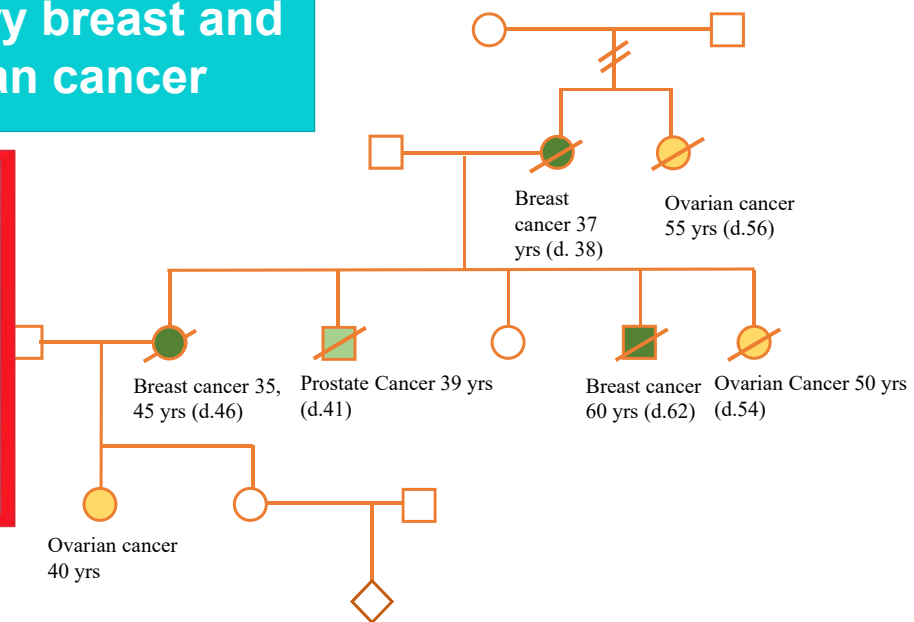
- Salpingo-oophorectomy and hysterectomy ~age 40
- Sub-total colectomy

### CHEMOPROPHYLAXIS

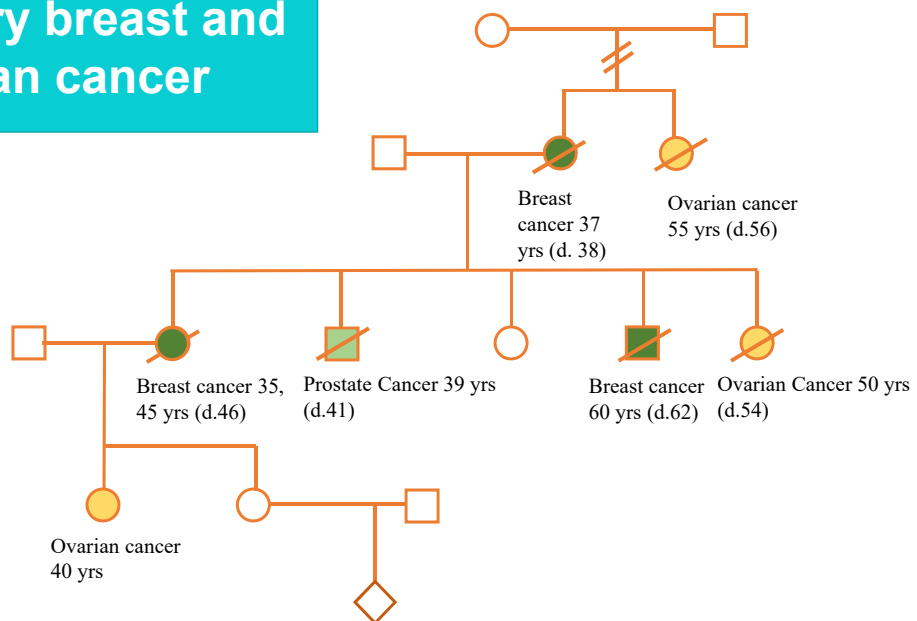
- Aspirin
  - dosing trial underway (CAPP3)
- Immunomodulation drugs

### VACCINES

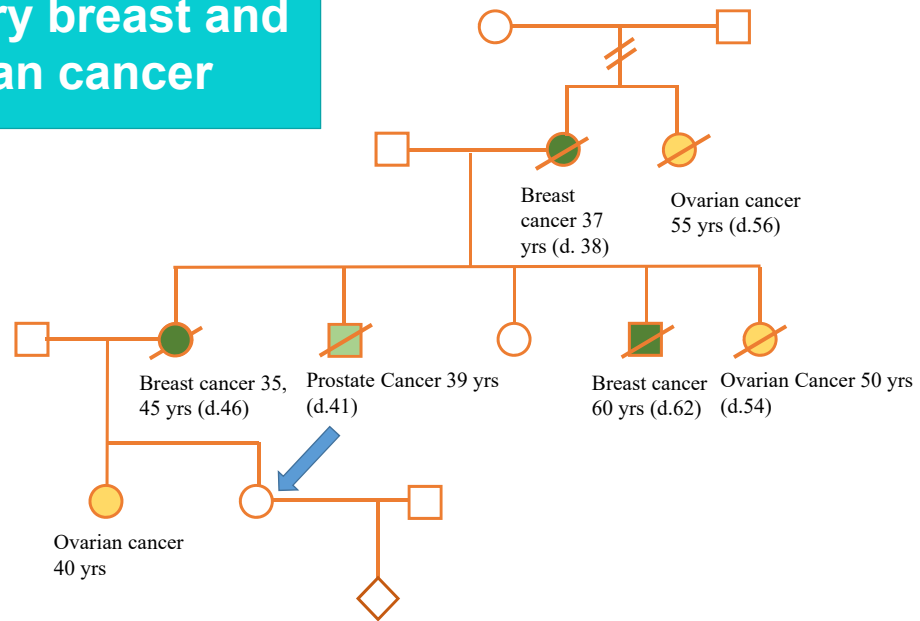
# Hereditary breast and ovarian cancer



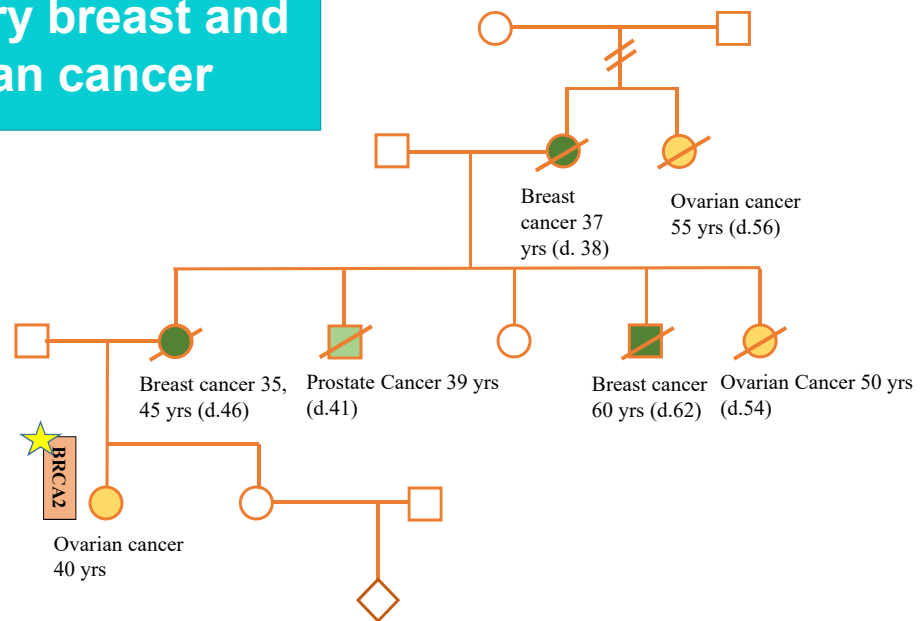
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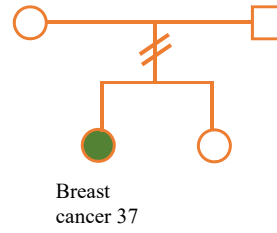
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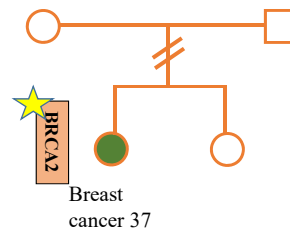
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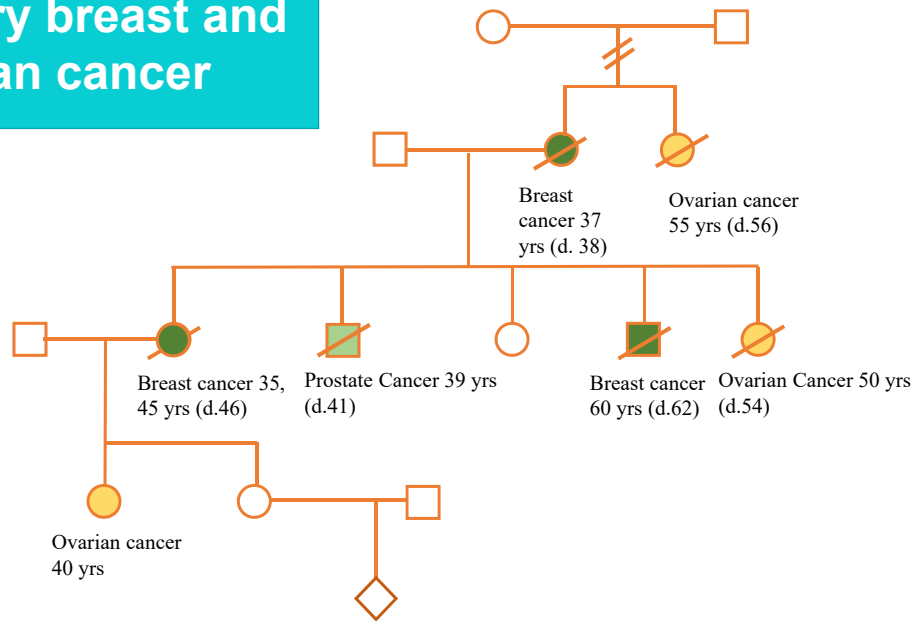


## Hereditary breast and ovarian cancer

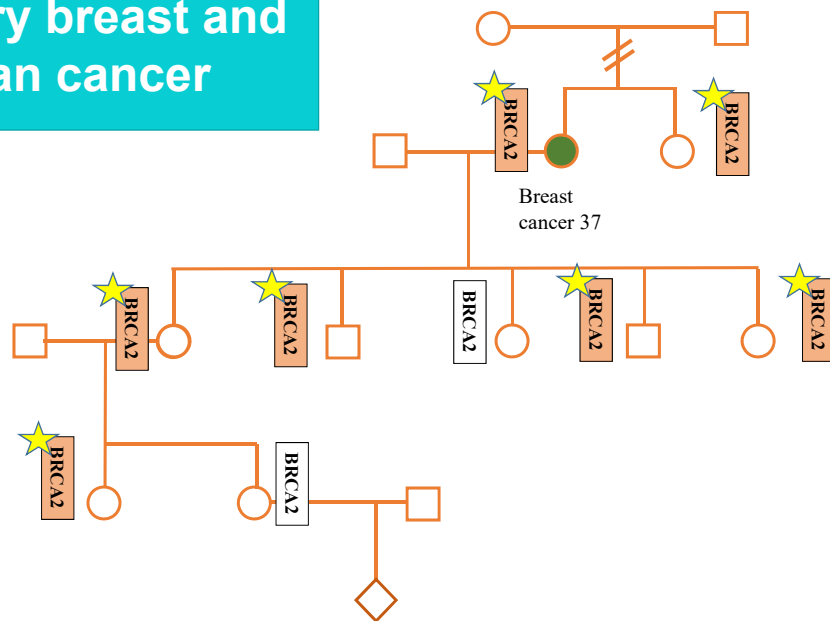




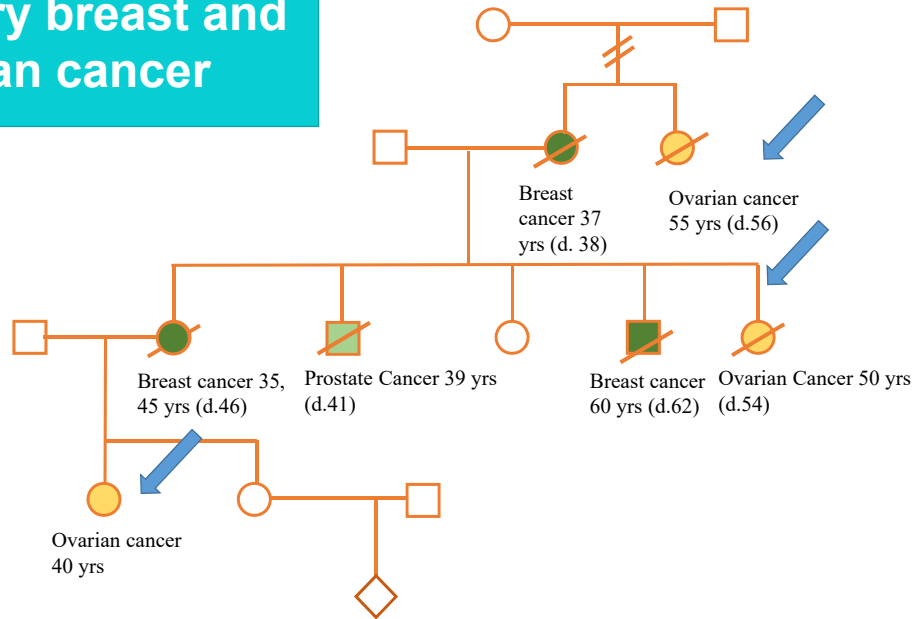
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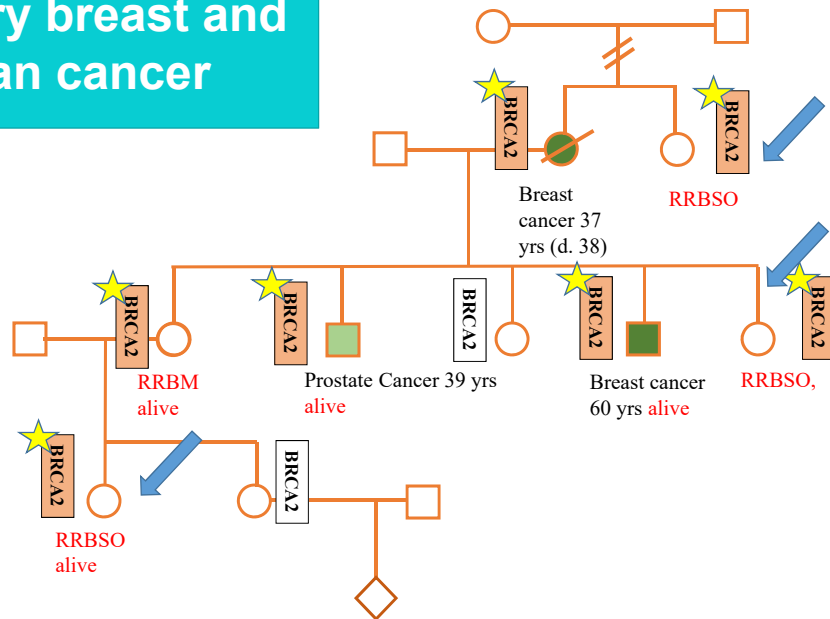
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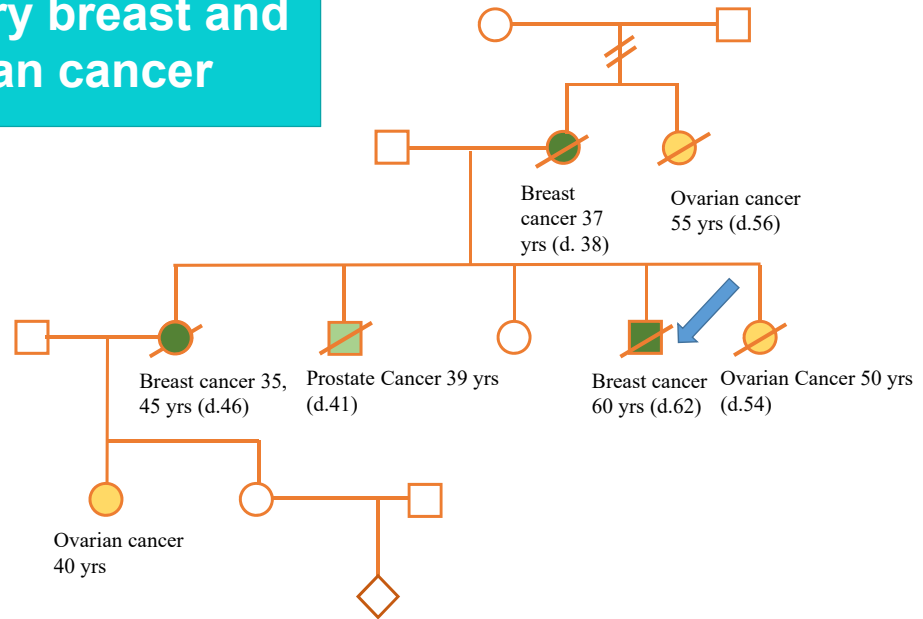
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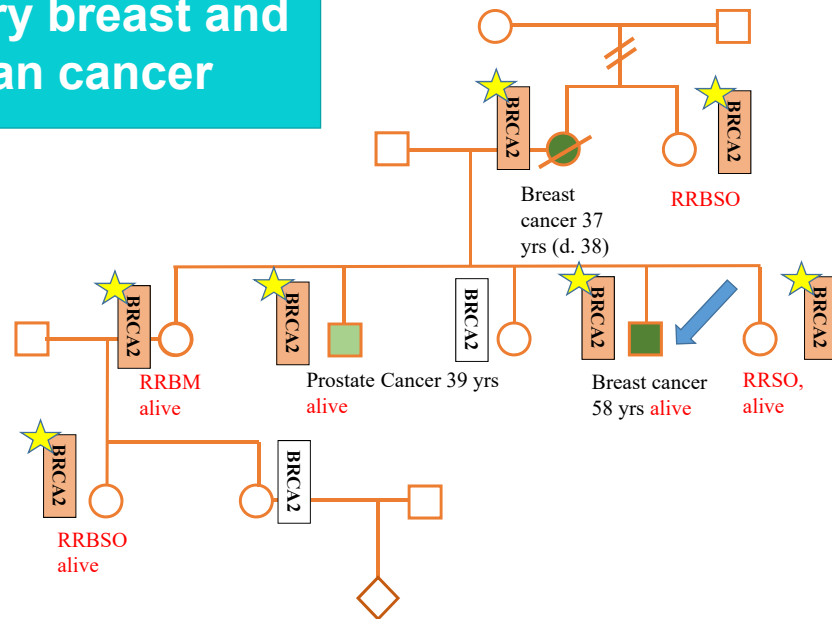
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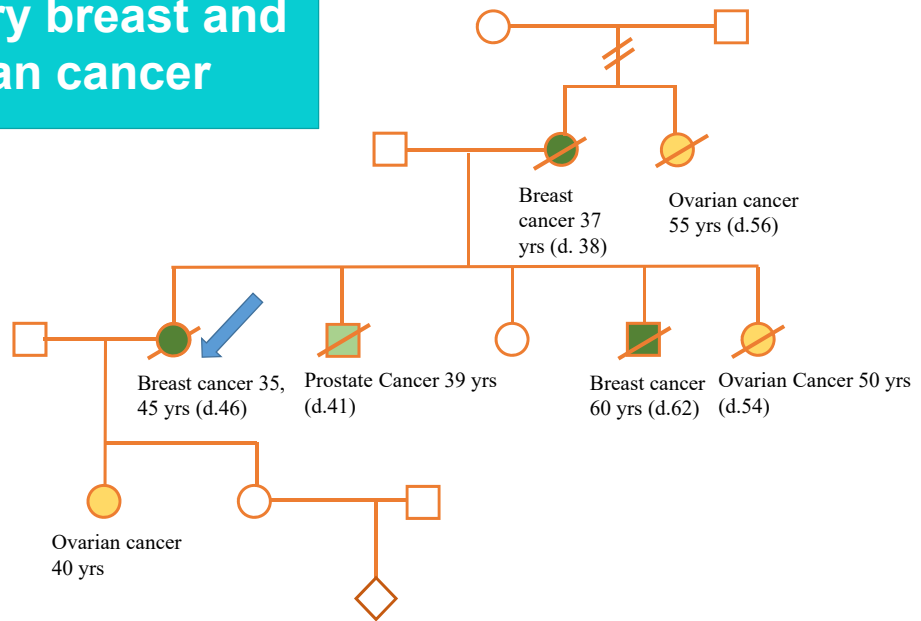
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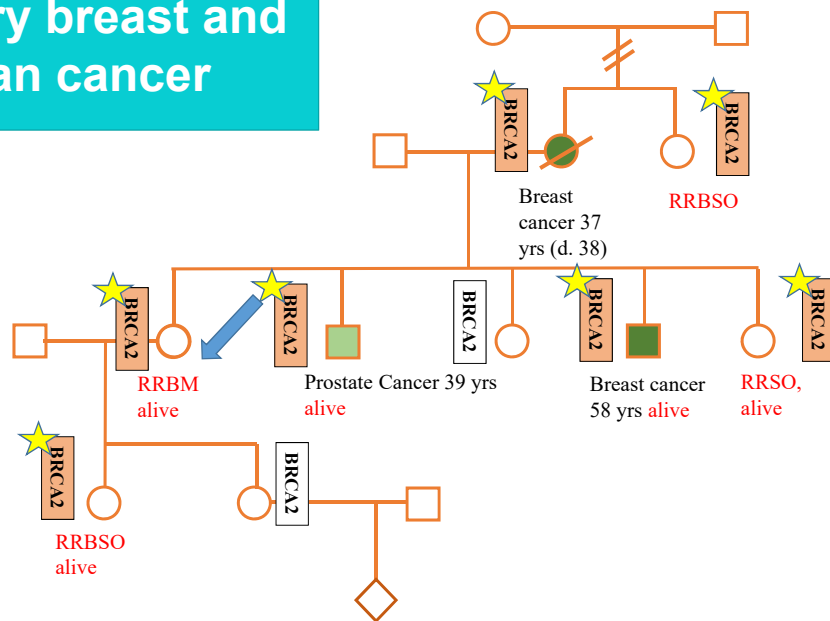
## Hereditary breast and ovarian cancer



## Hereditary breast and ovarian cancer



## Hereditary breast and ovarian cancer



# Screening, Early Detection, Prevention in BRCA1/BRCA2

## SCREENING AND EARLY DETECTION

- MRI and mammography annually from age 30

## PREVENTION

### SURGERY

- Salpingo-oophorectomy from age~40
- Preventative Bilateral Mastectomies

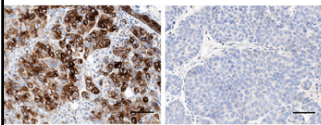
### CHEMOPROPHYLAXIS

- Tamoxifem
- RANK-Ligand inhibitors

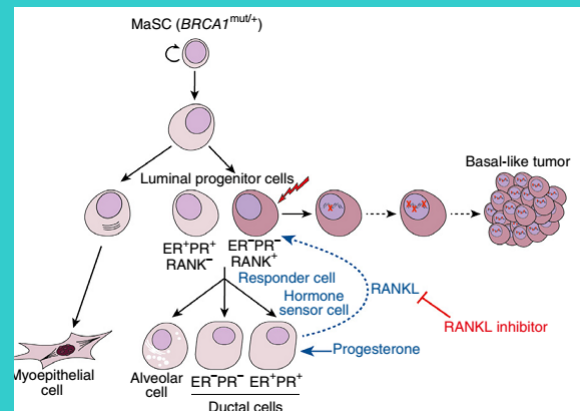
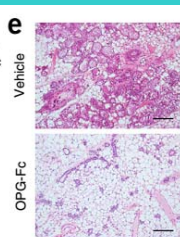
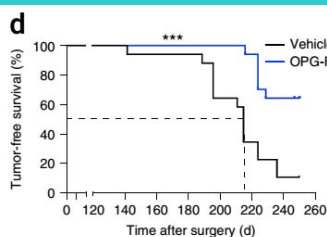
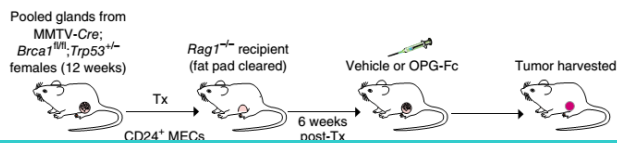
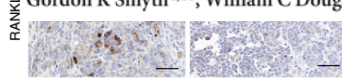


## RANK ligand as a potential target for breast cancer prevention in BRCA1-mutation carriers

MMTV-Cre; Brca1<sup>fl/fl</sup>; Trp53<sup>-/-</sup> Trp53<sup>-/-</sup>



**b** Emma Nolan<sup>1,2</sup>, François Vaillant<sup>1,2</sup>, Daniel Branstetter<sup>3,15</sup>, Bhupinder Pal<sup>1,2</sup>, Göknur Giner<sup>2,4</sup>, Lachlan Whitehead<sup>5</sup>, Sheau W Lok<sup>1,6,7</sup>, Gregory B Mann<sup>8,9</sup>, Kathleen Cuninghame Foundation Consortium for Research into Familial Breast Cancer (kConFab)<sup>10</sup>, Kathy Rohrbach<sup>3</sup>, Li-Ya Huang<sup>3</sup>, Rosalia Soriano<sup>3</sup>, Gordon K Smyth<sup>4,11</sup>, William C Dougall<sup>12,15</sup>, Jane E Visvader<sup>1,2,16</sup> & Geoffrey J Lindeman<sup>1,6,7,13,14,16</sup>



Nolan E et al. Nature Med epub 20 Jun 2016

## Testing for Cancer susceptibility genes has wide clinical utility

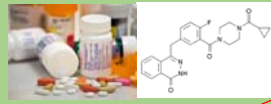
Enhanced Screening Early Detection and Prevention



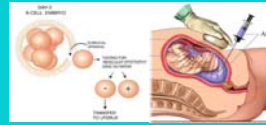
Information for relatives



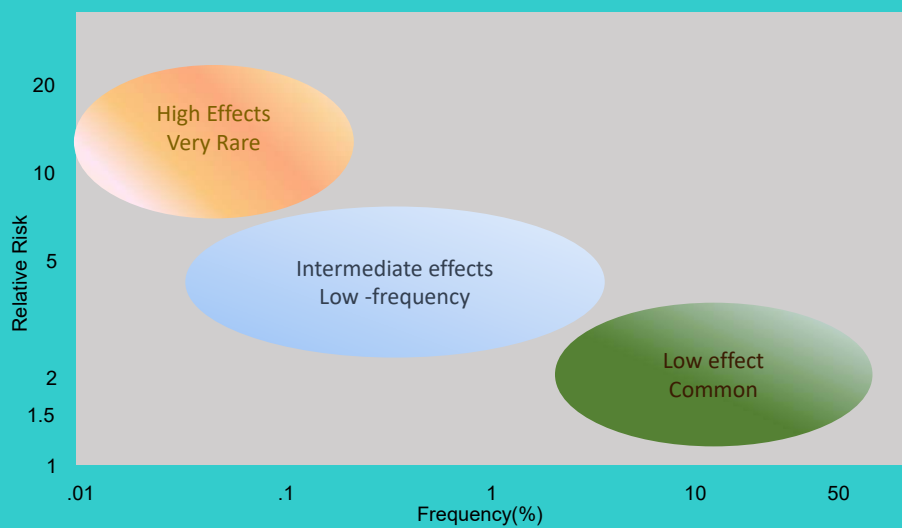
Cancer management: chemotherapy, targeted treatment and prognostic information



Reproductive decisions



## Genetic architecture of cancer susceptibility



## Genetic architecture of breast cancer susceptibility

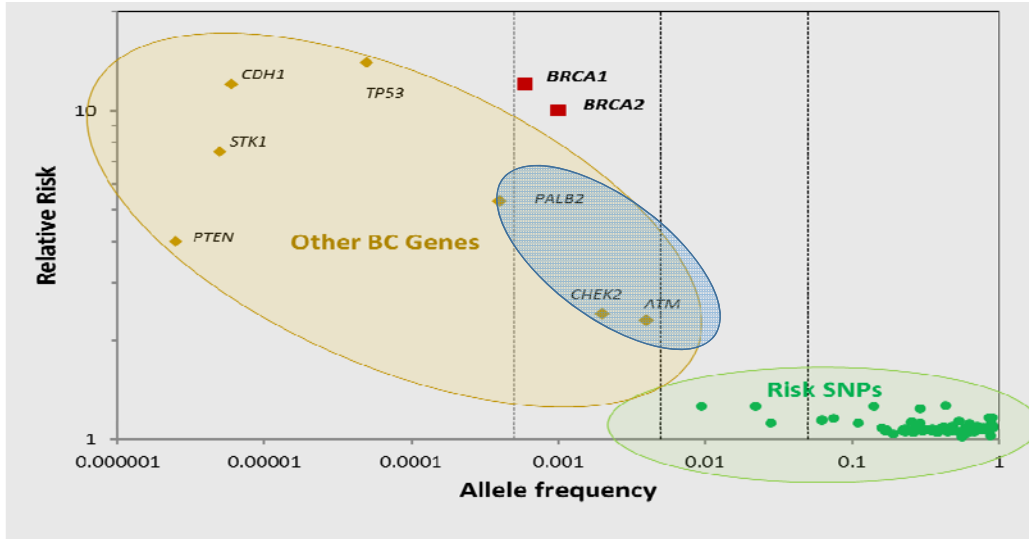


Image courtesy of Doug Easton

## Using genetic and non-genetic factors to tier breast cancer risk

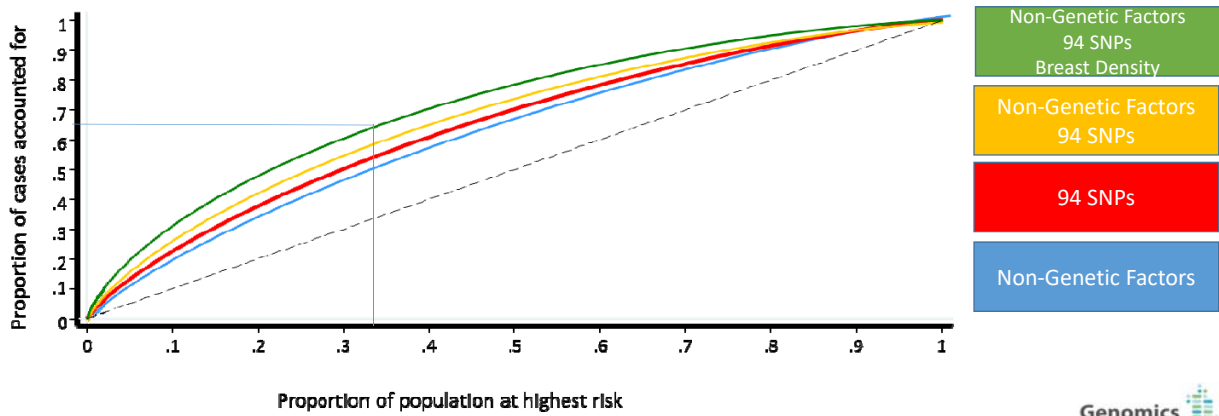


Image courtesy of Doug Easton

# Using genetic and non-genetic factors to tier breast cancer risk

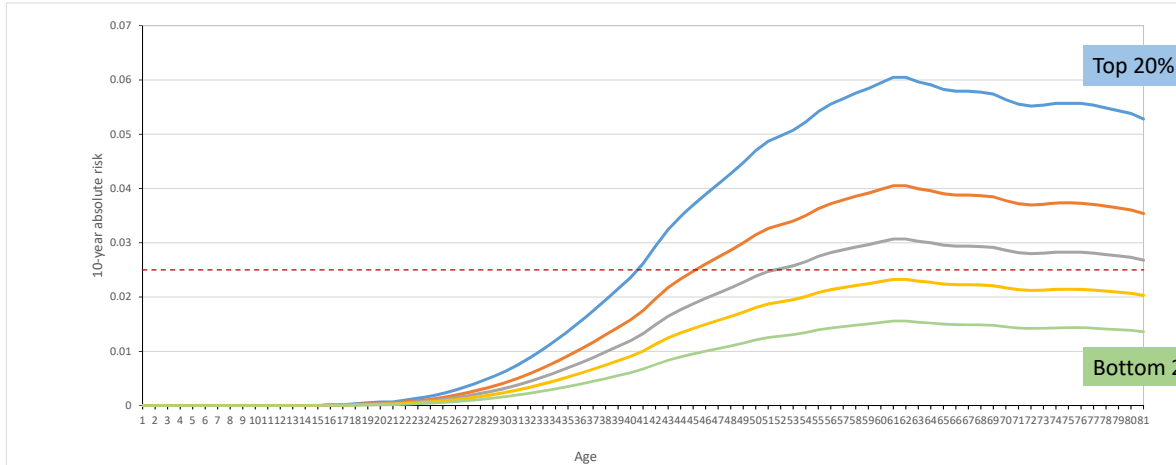


Image courtesy of Doug Easton

# Using genetic and non-genetic factors to target breast cancer screening

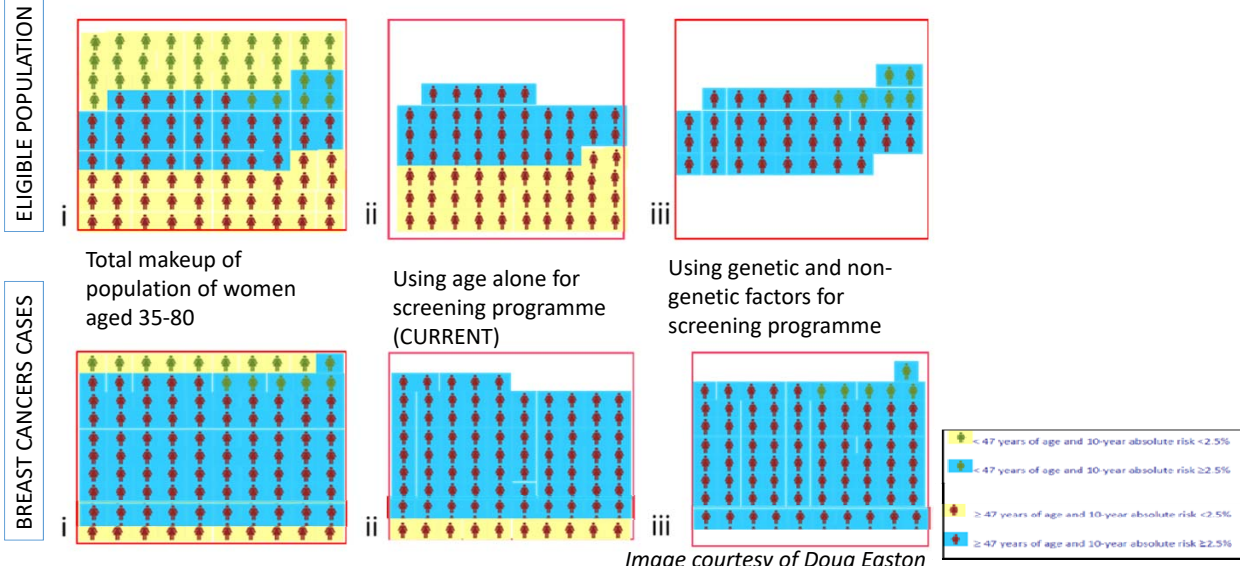


Image courtesy of Doug Easton



## Using genetic and non-genetic factors to tier breast cancer risk

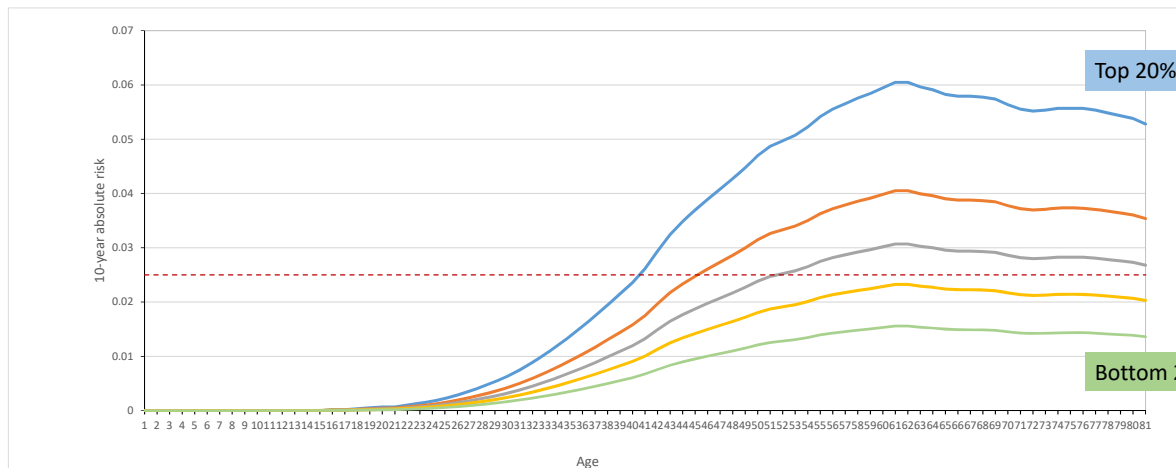


Image courtesy of Doug Easton

## Summary

- Genetics can help target resources for Early Detection and Prevention
- The majority of cancers occur in the minority of individuals at elevated genetic risk
- We should look for individuals carrying mutations in high penetrance cancer susceptibility genes (Lynch, BRCA1/2)
- Risk modelling combining genetics and non-genetic factors can be applied to direct screening resources in the population
- Colorectal cancer is a very tractable model for success in screening, prevention and early detection

## Questions/Challenges

- Can change our screening program to **take away** screening from those at lower genetic risk?
- Can we create '**registries**' of individuals at increased genetic risk
  - In order to manage them effectively
  - In order to learn which interventions are effective in which groups
  - Extension of section 251 for data linkage
- Will we fund the required **large-scale longitudinal genetic cohort studies** and **screening implementation studies (10-20 year)**